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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,230	01/20/2006	Philippe Erbs	1032751-000131	2237

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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/565,230	ERBS, PHILIPPE	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 35-55* is/are pending in the application.

4a) Of the above claim(s) *1-11,30-38 and 47-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-29,39-46 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03-20-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06-25-2009 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 1-31 and 35-55 are pending. Claims 12, 15 and 53 have been amended by Applicants' amendment filed on 06-25-2009. Claims 1-11, 30, 31, 35-38 and 47-52 were previously withdrawn from consideration as being directed to non-elected inventions pursuant to 37 CFR1.14(b), there being no allowable generic or linking claim.
3. Therefore, claims 12-29, 39-46 and 53-55 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn Rejections/objection in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' amendment of claim 12 to recite "a fusion protein comprising the polypeptide of SEQ ID NO: 2, rejection of claims 12-29, 39-46 and 53-55 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections/objection maintained in response to Applicants' arguments or amendments

New grounds of rejection

Claim Rejections - 35 USC § 103(a)

To the extent that the instant claims are drawn to an isolated nucleotide sequence encoding a fusion protein comprising the polypeptide of SEQ ID NO: 2 fused in frame with a polypeptide having cytosine deaminase activity, wherein said fusion protein has neither uracil phosphoribosyltransferase (UPRTase) or thymidine kinase activity, the following rejection applies.

Claims 12-17, 20, 22-29, 39-46 and 54-55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Erbs et al (WO99/54481, Date of Publication Oct. 28, 1999; see SCORE Search Results Details for Application 10565230 and Search Result 20080502_113223_us-10-565-230-1.p2n.rge. Result: No.1) in view of Kern et al (Gene, 1990, pp. 149-157, **see** SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.p2n.rge. Result **No. 4**). Citations are from the National Stage U.S. Patent No. 6,596,533. The National Stage is deemed an English language translation of the PCT).

Erbs et al., discloses an isolated nucleotide sequence encoding a fusion protein derived from the *Saccharomyces cerevisiae* cytosine deaminase (FCY1) and uracil phosphoribosyltransferase genes (FUR1), the chimeric protein was generated by fusing the *FCY1* and *FUR1* coding sequences in frame. In nonpreferred embodiments, Erbs discloses a polypeptide which comprises an amino acid sequence which is substantially as depicted in the SED ID NO: 2 sequence identifier, starting at the Met residue in position 1 and finishing at the

Val residue in position 373 (col. 5, lines 38-45). The chimeric protein generated exhibit both CDase activity (e.g., CDase encoded by the FCY1 gene) UPRTase activity (encoded by the FUR1 gene) (col. 2, lines 65-67, bridging to col. 3, lines 1-2) Note that fusion protein of SEQ ID NO: 2 of Erbs is identical to the fusion protein of the instant invention of SEQ ID NO:1 (SEQ ID NO:1 is 373 residue amino acid sequence) except that the Arg at position 183 of the Erbs et al., sequence has been replaced with a Ser in SEQ ID NO:1 of the invention (see SCORE Search Results Details for Application 10565230 and Search Result 20080502_113223_us-10-565-230-1.p2n.rge. Alignment Result: No.1)**(Current claim 12, in part)**. Also note that thymidine kinase activity results from expression of TK by the *TK* gene which is not the *FCY1* nor *FUR1* coding sequences, clearly indicating that *FCY1* and *FUR1* genes encoding the CDase and UPRTase enzymes have not TK activity (col. 1, lines 37-50). Moreover, Erbs discloses the UPRTase protein, or its fusion proteins (particularly with CDase), nucleic acids encoding them and derived recombinant vectors, virus particles and transformed cells are useful in human and veterinary medicine, for gene therapy or production of recombinant proteins (col. 3, lines 30-41; col. 6, lines 55-65; col. 11,lines 22-30) **(Current claims 40, 42 and 44)**. Viral vectors include vaccinia virus, in particular MVA, canarypoxvirus, and others (col. 7, lines 18-26). **(Current claims 14, 16, 17 and 55).** Erbs teaches that the transfectional efficiency and/or stability of the vector can be improved by cationic lipids (col. 6, line 50) **(Current claims 15 and 54)**. Expression of the FUR1deleted 105 is under the control of the early CMV promoter or other promoters (col. 16, line 34; col. 23, lines 25-35; col. 8, lines 30-62) **(Current claims 13, 20 and 24)**. Isolated vector with deleted regions which are essential for replication are disclosed throughout the whole document, for example at col. 7, lines 50-56; col. 24, lines col. 23, lines 15-23) (Current **claims**

22 and 23). In addition, Examples 7 discloses the combination of the FCU1 suicide gene and genes encoding cytokines including IFN-γ and IL-2 (col. 10, lines 49-52; col. 24, line 16) (**Current claim 25, 26 and 43**). Furthermore, Erbs et al., discloses methods for preparing viral particles wherein the defective essential functions are completed in trans by means of a complementing cell line (col. 9, lines 47-56; col. 7, lines 55-60; col. 10, lines 34-38;col. 11, lines 10-15; 9) ; (**Current claims 27, 28, 29, 39, 41, 45 and 46**). Moreover, Erbs et al., discloses that the fusion polypeptide may be a deletion mutant of a native UPRTase. The deletion is preferably located in the N-terminal region of the original UPRTase including deletions affecting one or more residues which may or may not be continuous in the primary structure (col. 4, lines 10-25).

Erbs et al., et al., does not particularly teach a polypeptide sequence having 100% homology to SEQ ID NO:2 (SEQ ID NO:2 is 373 residue amino acid sequence).

However, at the time the invention was made, the nucleotide sequence of the yeast FURI gene and deduced aa for UPRTase were commonly used sequences known in the art as evidenced by Kern et al.,. Indeed, Kern et al discloses a 753 bp open reading frame encoding a UPRTase protein of 251 aa. The native UPRTase protein contains 2 Met residues, one at position 1 and the second at position 36. Moreover, Kern discloses single bp changes located in different regions of the gene leading to the lost of UPRTase activity, including a *fur1 -8* allele wherein an Arg^{61} residue is changed into Ser (p. 155, col. 2, paragraph 1). It is noted that this Arg residue corresponds to the aa at position 26 in SEQ ID NO:2 (see SCORE Search Results Details for us-10-565-230-2.p2n.rge. See Result **No. 4).** Furthermore, Kern et al., discloses that UPRTase enzyme and the mutants UPRTase enzymes generated do not carry a second activity in addition to UPRTase activity (p. 156, col. 1, paragraph 2)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art to modify the isolated the fusion protein of Erbs of SEQ ID NO:2 encoded by the FCY1 and FUR1 genes having the CDase and UPRTase activities, with a mutated FUR1 gene that comprises a single mutation of Arg to Ser as taught by Kern, particularly because Kern discloses a loss of UPRTase activity by replacing the Arg residue at position 61 for a Ser in an attempt to generate a fusion protein with CDase activity but not UPRTase activity. Moreover, the state of the art teaches that it is well established in the art to make and test oligos of different sizes in the design of drugs to interfere with gene expression of a known sequence. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. As all the elements where known in the prior art, one of ordinary skill in the art would have had a reasonable expectation of success in making fusion protein comprising the polypeptide of SEQ ID NO:2 fused in frame with second polypeptide having cytosine deaminase activity wherein the fusion protein has not UPRTase activity as claimed by combining the disclosure of Erbs teaching the isolated the fusion protein encoded by the FCY1 and FUR1 genes with CDase and UPRTase activities with a mutated FUR1 gene lacking UPRTase activity to generate a fusion protein having CDase activity but not UPRTase activity.

Response to Applicants' arguments as they apply to rejection of claims 12-17, 20, 22-29, 39-46 and 54-55 under 35 U.S.C. 103(a)

At page 10 of the remarks filed on 06-25-2009, Applicants, essentially argue that :1) Erbs describes a fusion protein FCU1 (SEQ ID NO:2) corresponding to the fusion in frame of a polypeptide having UPRTase activity encoded by a truncated FUR1 Δ105 gene of SEQ ID NO:1

with a polypeptide having CDase activity, Erbs doe not teach that the substitution or an Arg residue at position 183 with a Ser residue in SEQ ID NO: 2, and therefore the FCU1-8 of the invention, 2) Example 5 of Erbs, teaches that the fusion polypeptide FCU1 with an equivalent UPRTase activity observed whether the gene is in the fused form (pCI-neoFCU1) or in the unfused form (pCI-neoFUR1A105); and that the CDase activity is increased by a factor of 10 when the gene is in the fused form as compared with the unfused FCY1 gene, and 3) Kern discloses fur1 mutants each containing a single point mutation which result in lost of UPRTase activity; however Kern does not teach or suggest the fusion protein of the instant invention. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1) and 2), the fact that in preferred embodiments Erbs discloses a chimeric fusion protein which is produced by the hybrid FCY1::Δ105 gene which results from the in-frame fusion of the FCY1 and truncated FUR1 genes exhibiting a CDase activity increased by a factor of 10 when the gene is in the fused form as compared with the unfused FCY1 gene is not disputed. However, in nonpreferred embodiments Erbs discloses a chimeric protein comprising both the FCY1 and FUR1 genes encoding the CDase and UPRTase enzymes exhibiting CDase activity and UPRTase activity (encoded by the FUR1 gene) (col. 2, lines 65-67, bridging to col. 3, lines 1-2). The Erbs et al. Patent only needs to make one credible assertion of specific utility for the claimed invention to satisfy the 35 U.S.C. 101 and 35 U.S.C. 112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility. See MPEP 2107.02, under the heading "The Claimed Invention Is the Focus Of The Utility Requirement". Hence, the disclosure is fully enabling for the scope embraced by the claims. Moreover, the disclosure of the Erbs et al. Patent does not have to exemplify all the nonpreferred

embodiments to be enable, anticipation requires only an enabling disclosure. In re Donohue, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. Bristol-Myers, 246 F.3d at 1379; see also In re Donohue, 766 F.2d at 533. Addtionally, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Regarding 3), the yeast FURI gene and deduced structure for UPRTase activity was known in the art. Kern discloses a mutant the FUR1 gene of *Saccharomyces cerevisiae* encoding a mutant UPRTase wherein the Arg^{61} residue is changed into Ser, said mutation corresponding to the Arg → Ser change at residue position 183 in the claimed FCY1 and FUR1 fusion protein of SEQ ID NO:2 of Erbs (SEQ ID NO:2 of Erbs is 373 residue amino acid sequence). The site mutation Arg → Ser in the UPRTase enzyme abrogates UPRTase activity. So coexpression of a mutant UPRTase enzyme (e.g., Arg → Ser) and a CDase enzyme having cytosine deaminase activity should be reasonably expected to result in lost of uracil phosphoribosyltransferase activity; there is not evidence that by generating the fusion protein, a CDase enzyme may rescue the lack of UPRTase functionality. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Erbs et al (WO99/54481, Date of Publication Oct. 28, 1999; see SCORE Search Results Details for Application 10565230 and Search Result 20080502_113223_us-10-565-230-1.p2n.rge. Result: No.1) in view of Kern et al.(Gene, 1990, pp. 149-157, **see** SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.p2n.rge. Result **No. 4**) as applied to claim 12-17, 20, 22-29, 39-46 and 54-55 above, and further in view of Faure et al., (Date of publication, 1986, EP 0206920; An official translation of the document has been requested).

The teachings of Erbs and Kern are outlined in the paragraphs above.

The combined disclosure of Erbs and Kern fails to teach a promoter of the thymidine kinase (TK) that is 7.5K gene.

However, at the time the invention was made, Faure et al., exemplifies cloning and expression of the IFN-γ under the control of the TK of 7.5K (page 3, lines 10-15; page 4, line 20-25).

Therefore, it would have been obvious for one of ordinary skill in the art to have employed any of the known viral vector promoters for sufficient expression of a gene of interest including a TK of 7.5K, as exemplified by Faure et al., in the viral vector taught by Erbs and Kern in order to target expression of a gene of interest in a cell with a reasonable expectation of success, particularly since Faure evidences successfully expression of IFN-γ in Vero cells by using a viral vector operably linked to the TK of 7.5K. Thus, one of ordinary skill in the art would have been motivated to have employed any of the known specific promoters, including TK of 7.5K, as exemplified by Faure, in the viral vector taught by Erbs and Kern in order to express a gene of interest in a cell.

Claims 18 and 19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Erbs et al (WO99/54481, Date of Publication Oct. 28, 1999; see SCORE Search Results Details for Application 10565230 and Search Result 20080502_113223_us-10-565-230-1.p2n.rge. Result: No.1), in view of Kern et al.(Gene, 1990, pp. 149-157, **see** SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.p2n.rge. Result **No. 4**) as applied to claim 12-17, 20, 22-29, 39-46 and 54-55 above and further in view of Sutter et al., (FEBS Letters, 1995, pp 9-12) and Carroll (Vaccine 1997, pp. 387-394).

The teachings of Erbs and Kern are outlined in the paragraphs above.

The combined disclosure of Erbs and Kern fails to teach the MVA genome with deletions of I, II, III, IV and IV .

However, at the time the invention was made, the complete genome DNA sequence of the highly attenuated MVA was well known in the art as evidenced by Sutter et al., including precise restriction maps and naturally occurring deletion II, (See page 10, Fig, 1. Schematic representation of map of the genome of MVA). Likewise, Carroll evidences the use of MVA as an effective recombinant vector for expression of heterologous genes in mammalian cells, particularly vectors with the deleted region III of MVA (p. 387, col. 2, paragraph 2). Furthermore, Carroll discusses the use of recombinant MVA an immunogen in cancer immunotherapy, in part, because of its safety (p. 391, col. 1 and 2) .

Therefore, in view of the benefits of using a modified MVA as a safe vector for the development of recombinant cancer vaccines as taught by Sutter and Carroll, it would have been obvious for one of ordinary skill in the art to have modify the viral vector disclosed by Erbs and

Kern with a modified MVA comprising a deletion of the II or III region for use as a safe vector in anti-cancer vaccines. The claims would have been obvious because a person of ordinary skill has a good reason to pursue the known options in his grasp. In turn, because an isolated recombinant modified MVA has the proprieties predicted by the prior art it would have been obvious to make the modified MVA with insertion of a nucleotide sequence at known naturally occurring deletions of its genome.

Response to Applicants' arguments as they apply to rejection of claims 18 and 19 under 35 U.S.C. 103(a)

At page 11 of the remarks, Applicants allege that Sutter describes MVA vectors Sutter et al. describes MVA vectors expressing bacteriophage T7 RNA polymerase, Carroll et al. describes MVA vectors expressing B-galactosidase, and Faure et al. describes poxviruses expressing IFN-y. None of these three references teach or suggest vectors comprising a nucleotide sequence encoding the FUR1A 105 polypeptide having UPRTase activity; the FUR1A 105 polypeptide including the Arg to Ser substitution having no UPRTase activity; or the FUR1A105 polypeptide including the Arg to Ser substitution and fused in frame with a polypeptide having CDase activity encoded by the FCY1 gene, where the fusion protein has neither UPRTase nor TK activity.

Applicants' arguments have been respectfully considered but have not been found persuasive for the reasons already of record as set forth in the Office action of 03-25-2009 and the reasons set forth in the paragraphs above.

Other art for comment

The following art are cited to complete the record:

Erb et al., (2000; Cancer Research; In vivo cancer gene therapy by adenovirus-mediated transfer of a bifunctional yeast cytosine deaminase/uracil phosphoribosyltransferase fusion gene pp. 3813-3822).

Conclusion

Claims 12-29, 39-46 and 53-55 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633